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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/622,613 | 07/31/2001 | Susanna M. Rybak | 15280-3431US | 8380 |

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| EXAMINER |
|---|
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| ART UNIT | PAPER NUMBER |
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| 1642 | |

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/622,613 | RYBAK ET AL. | |
| | Examiner | Art Unit | |
| | MISOOK YU, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *20-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11, 14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's election with traverse of group I, claims 1-19 and 34-44 with species SEQ ID NO:2 in Paper No. 15 is acknowledged. The traversal is on the ground(s) that all of the three groups stem from a common concept and theory and examination of the claims together would not impose an undue burden on the examiner. Further, applicant alleges that the examiner refuses to examine claim 1 by asking applicant to elect a species of claim 1. This is not found persuasive because a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).) Further, this examiner does not understand the basis for applicant's allegation that this examiner refuses to examine claim 1. Claim 1 is a generic claim and applicant's response that SEQ ID NO:2 reads on claims 1-19 and 34-44, clearly indicates that SEQ ID NO:2 is a species of the generic claim 1. Examination of a species that belongs to a generic claim is not refusing to examination of the generic claim.

Unity of invention involves special technical feature, which is feature that is an advance over the prior art. In claim 1, the special technical feature is seen as specific

amino acids at specific positions, i.e. an amino terminal end, 11, 21, 85, 103 through alignment with reference to those specified positions of SEQ ID NO:2. Note also the Election/Restrictions mailed on 8/13/2002. Ribonuclease activity and substantial identity to SEQ ID NO:2 are not special technical feature, being known in the art. Note the cited references in the search report. Elected SEQ ID NO:2 does not have the special technical feature specified in claim 1, does not have aspargine (Asn) at position 21, therefore unity of invention is lacking between elected SEQ ID NO:2 and the general invention of claim 1.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-44 are pending. Claims 20-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Claims 34-44 are examined to extent of elected species, SEQ ID NO:2.

### *Specification*

The disclosure is objected to because it, for example page 9 line 15, contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, 36, and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 recites "antineoplast" but it is not clear what the metes and bounds are for the term. The term is not recognized in the art and the specification does not define it.

Claim 44 recites "LL2" but it is not clear what the metes and bounds are for the term. Is this a trademark name that could be purchased from a vendor or a specific antibody produced by a specific hydridoma cell line? For the purpose of this office action, this examiner will assume LL2 is a monoclonal antibody produced by a hybridoma cell line. However, this treatment does not relieve applicant the burden of responding to this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims **34-37** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 34-36 are drawn to pharmaceutical composition comprising SEQ ID NO:2 and claim 37 is drawn to pharmaceutical composition comprising a cytotoxic reagent comprising SEQ ID NO:2. Inherent in pharmaceutical is in vivo use and the specification indicates the claimed pharmaceutical composition is used for cancer treatment. The specification at page 44 and 45, especially Table II says that RecRaPLR1 (SEQ ID NO:2?) has cytotoxic activity to several cancer cell lines in vitro. The bottom half of the specification at page 44 says that the cytoxic activity was measured according to Rybak et al (1991, J. Biol. Chem. Vol. 266, pages 21202-7, abstract only), which indicates that SEQ ID NO:2 (RecRaPLR1) was linked to antibodies to the transferring receptor via disulfide bond in order for the ribonuclease to enter the in vitro cells.

One cannot extrapolate the teaching of the specification to the claimed invention because the specification does not teach that the claimed pharmaceutical compostion

could be used of in vivo cancer treatment. The *in vitro* demonstration of protein synthesis inhibition of cancer cells in vitro with the transferin receptor antibody linked SEQ ID NO:2 cannot be correlated to the invention as claimed, because the *in vitro* assay the cytotoxic agent is in contact with target cells and are not subjected to the defense of the body. In addition, characteristics of cultured cell lines generally differ significantly from the characteristics of in vivo primary cancers or metastatic cancers. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, based on the cell culture data presented in the specification, it could not be predicted that either SEQ ID NO:2 or transferring receptor antibody linked SEQ ID NO:2 could kill tumor cells *in vivo*. In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion

of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation.

Further, one cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anticancer ***drug discovery for cancer therapy is highly unpredictable***, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting

task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

The specification provides insufficient guidance, and provides no working examples of a treatment in vivo which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation, and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed invention with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Claim **38** is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is drawn to method of killing cancer cells by contacting said cells with SEQ ID NO:2. The specification teaches that SEQ ID NO:2 is a ribonuclease protein and can be used to decrease protein synthesis when it is inside the cancer cells. The specification at bottom half of page 44 indicates that applicant used antibody to cell surface receptor in order for SEQ ID NO:2 to enter the cells. The specification does not teach any other way of targeting SEQ ID NO:2 into cells. It is well known in the art that crossing membrane barrier of cell is not a trivial matter. The

specification does not teach how to make how to target SEQ ID NO2 to to cytosol of a cell. Berg et al (05 March 1999, Cancer Research 59, 1180-1183) teach at the abstract, 1st paragraph column 1 and 5th paragraph column 2 of page 1181 that targeting macromolecules to cytosol is not an easy task.

The specification provides insufficient guidance, and provides no working examples of a treatment in vivo which would provide guidance to one skilled in the art to use the claimed invention without undue experimentation, and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed invention with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to practice the claimed invention.

Claim **44** is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 44 recites a specific antibody produced by a specific hybridoma cell line.

It is apparent that the recited antibody is required to practice the claimed invention, because it is specifically required in the claim. As required elements it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the cell lines listed in claim 7. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the antibody, and they do not appear to be readily available material. Deposit of the cell lines that produce the antibody would satisfy the enablement requirements of 35 U.S.C. 112. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or

her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

Claims **39-43** rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of killing cancer cells using transferring-receptor antibody linked SEQ ID NO:2, does not reasonably provide enablement for method of killing cancer cells using any other cytotoxic reagent comprising SEQ ID NO:2. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a method of killing cancer cells using cytotoxic agent comprising SEQ ID NO:2.

The bottom half of the specification at page 44 says that the cytoxic activity was measured according to Rybak et al (1991, J. Biol. Chem. Vol. 266, pages 21202-7, abstract only), which indicates that SEQ ID NO:2 (RecRaPLR1) was linked to antibodies to the transferring receptor and SEQ ID NO:2-transferrin receptor antibody could kill cancer cells.

One cannot extrapolate the teaching of the specification to the claims because both SEQ ID NO:2 and the other part of cytotoxic reagent seem to be proteins and it is well known in the art that even slight modifications in a peptide or protein structure and can have significant and unpredictable effects on biological activity. Newton et al (a copy provided with search report, 1998, Biochemistry, vol. 1998, pages 5173-5183), and Boix et al (a copy provided with search report, 1996, J. Mol. Biol. Vo. 257, pages 992-1007) teach even a single amino acid change in a ribonuclease markedly influence biochemical and biological activities of a ribonuclease. Further Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The specification does not teach what kinds of structural modification would be tolerated by SEQ ID NO:2 in order to retain the cytotoxic activity of SEQ ID NO:2.

Considering the limited teachings in the specification, and unpredictability of protein chemistry in the art, it is concluded that undue experimentation would be necessary to practice the full scope of the invention.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
October 31, 2002

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800
1600